

PATENT SPECIFICATION

NO DRAWINGS

Inventors: EMILIO TESTA, LUIGI FONTANELLA and GIULIO MAFFII



858.038

Date of filing Complete Specification: Oct. 14, 1959.

Application Date: Dec. 22, 1958.

No. 41323/58.

Complete Specification Published: Jan. 4, 1961. ✓

Index at acceptance:—Class 2(3), B4(A4:K), C3A14B(3D:8A).

International Classification:—C07d.

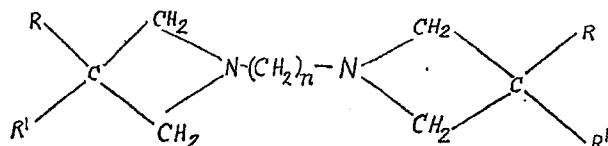
COMPLETE SPECIFICATION

Polymethylene Bis-Azetidines

We, LEPETIT S.P.A., an Italian Body Corporate, of 10, Via Roberto Lepetit, Milano, Italy, do hereby declare the invention, for which we pray that a patent may be granted 5 to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

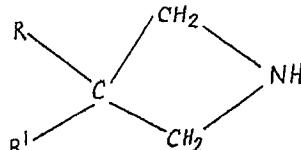
The invention is concerned with new pharmacologically active compounds. More particularly the invention relates to polymethylene-bis-azetidines of the formula:—

10



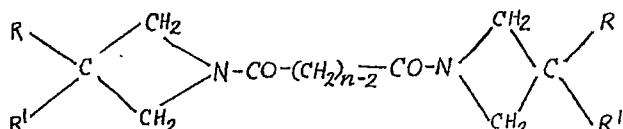
wherein R and R' represent alkyl or aryl radicals, n is an integer from 3 to 10 inclusive, and their quaternary ammonium salts. 15

The compounds of the invention are best prepared by reacting two moles of a di-substituted azetidine of the formula:—



20 wherein R and R' have the above significance with one mole of an appropriate alpha, omega-polymethylenedicarboxylic acid chloride in the presence of a tertiary base, such as tri- ethylamine or trimethylamine at room temperature. After diluting the reaction mixture with water, the formed diamide of the formula:—

25



30 separates and is isolated and hydrogenated with lithium aluminium hydride in an inert organic solvent. The obtained polymethylene-bis-azetidine is then converted, if desired, into a quaternary salt, such as the bis methyl iodide or the bis methyl chloride.

The compounds of the invention have proved to be useful as ganglionic blocking agents, sedatives and antispasmodics.

35

The following non-limitative examples are illustrative of the invention.

[Price 3s. 6d.]

Price 3s.

EXAMPLE I

1,6 - bis - (3 - Ethyl - 3 - phenyl - 1 - azetidine) - hexane.

5 Into a mixture of 10 g. of 3-ethyl-3-phenyl-azetidine and 10 ml. of trimethylamine 6 g. of adipyl chloride are gradually added without exceeding 0° C. After standing for about half an hour the reaction mixture is poured into ice water and the precipitate is collected and dried. Yield 6.5 g. of adipyl-bis 3 - ethyl - 3 - phenyl - azetidine, m.p. 149-150° C.

10 The above intermediate is dissolved in 50 ml. of tetrahydrofuran, then a suspension of

15 3 g. of LiAlH₄ in 20 ml. of tetrahydrofuran is added. The mixture is warmed for 2.5 hours at about 50° C., then it is treated with a few millilitres of a 20 percent solution of ammonium chloride. After filtration the 20 filtrate is dried over anhydrous sodium sulphate and evaporated to dryness. The residual oil crystallises on standing. Yield 6 g., m.p. 60-62° C.

25 To obtain the bis methyl iodide 2.5 g. of the compound are dissolved in 50 ml. of anhydrous ethyl ether, then 1.76 g. of methyl iodide are added. A crystalline product separates gradually and is collected and dried.

Yield 2.3 g., m.p. 100° C. (dec.).

EXAMPLE II.

30 1,6 - bis - (3,3 - Diethyl - 1 - azetidino) - hexane.

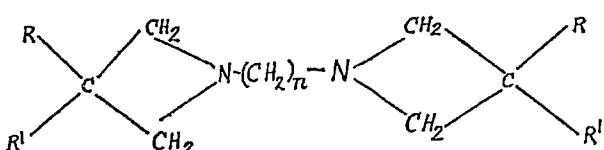
35 Into a mixture of 27 g. of 3,3-diethylazetidine and 25 ml. of triethylamine 22 g. of adipyl chloride are gradually added without exceeding 0° C. After standing for about one hour the reaction mixture is poured into ice water and extracted with ethyl ether. The solvent is removed and the residual oil is distilled collecting at 200-210°/0.2 mm. Yield 30 g. of adipyl-bis-3,3-dimethylazetidine, m.p. 40-45° C.

40 The above intermediate (3.25 g.) is dissolved in 20 ml. of tetrahydrofuran and hydrogenated with a suspension of LiAlH₄ in tetrahydrofuran as described in Example I. After evaporation of the solvent the residual oil is distilled collecting at 135-145° C./0.2-0.4 mm. Yield 2.5 g.

45 The bis methyl iodide, prepared by the process of Example I, melts at 180-181° C. (dec.).

WHAT WE CLAIM IS:—

50 1. A polymethylene-bis-azetidine of the formula:—

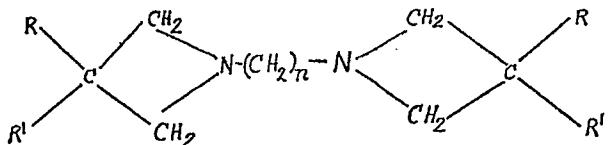


55 wherein R and R¹ represent alkyl or aryl radicals, n is an integer from 3 to 10 inclusive, and their quaternary ammonium salts.

60 2. 1 - 6 - Bis - (3 - ethyl - 3 - phenyl - 1 - azetidino) - hexane.

3. 1,6 - Bis - (3,3 - diethyl - 1 - azetidino) - hexane.

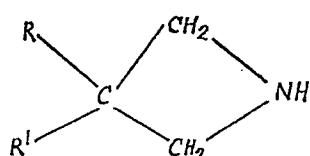
4. A process for preparing polymethylene bis-azetidines of the formula:—



65 wherein R and R¹ represent alkyl or aryl radicals, n is an integer from 3 to 10 inclusive, and their quaternary addition salts, which comprises reacting 2 moles of a di-substituted azetidine of the formula:—

70 wherein R and R¹ have the above significance, with 1 mole of an appropriate alpha,omega - polymethylenedicarboxylic acid chloride in the presence of a tertiary base at room temperature, diluting the reaction mixture with water, collecting the precipitate and hydrogenating it with lithium aluminium hydride in an inert organic solvent, and converting, if desired, the obtained polymethylene-bis-azetidine into its quaternary ammonium salts.

75 5. Process for the preparation of a polymethylene-bis-azetidine of the formula:—



80 5. Process for the preparation of a polymethylene-bis-azetidine of the formula:—

85

30

35

40

45

50

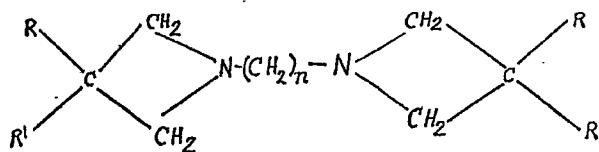
55

60

75

80

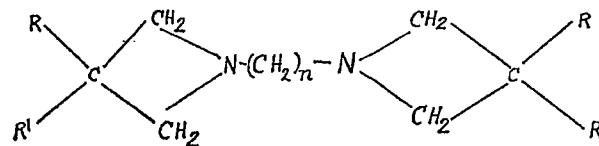
85



5 wherein R and R¹ represent alkyl or aryl radicals, n is an integer from 3 to 10 inclusive, and the quaternary ammonium salts thereof substantially as herein described with

reference to any of the examples.

6. A polymethylene-bis-azetidine of the formula:—



10 wherein R and R¹ represent alkyl or aryl radicals, n is an integer from 3 to 10 inclusive, and the quaternary ammonium salts thereof when prepared by a process as claimed in claim 4 or 5.

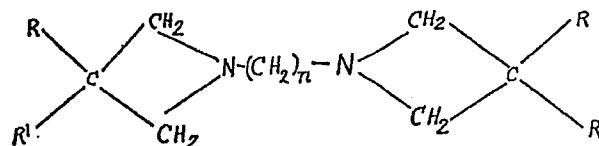
For the Applicants:—
GILL, JENNINGS & EVERY,
Chartered Patent Agents,
51/52 Chancery Lane,
London, W.C.2.

PROVISIONAL SPECIFICATION

Polymethylene Bis-Azetidines

15 We, LEPETIT S.P.A., an Italian Body Corporate, 10 Via Roberto Lepetit, Milano, Italy, do hereby declare this invention to be described in the following statement:—

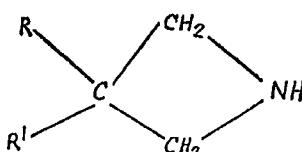
The invention is concerned with new pharmacologically active compounds. More 20 particularly the invention relates to polymethylene-bis-azetidines of the formula:—



25 wherein R and R¹ represent alkyl, aryl or aralkyl radicals, n is an integer from 3 to 10 inclusive, and their quaternary addition salts.

The compounds of the invention are best prepared by reacting two moles of a disubstituted azetidine of the formula:—

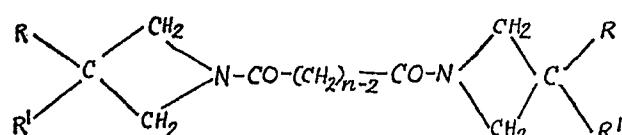
30



35 wherein R and R¹ have the above significance with one mole of an alpha,omega-poly-methylenedicarboxylic acid chloride in the presence of a tertiary base, such as triethyl-

amine or trimethylamine at room temperature. After diluting the reaction mixture with water, the formed diamide of the formula:—

40



separates and is isolated and hydrogenated with lithium aluminium hydride in an inert organic solvent. The obtained polymethylene-bis-azetidine is then converted, if desired,

45 into a quaternary salt, such as the bis methyl iodide or the bis methyl chloride.

The compounds of the invention have proved to be useful as ganglionic blocking

agents, sedatives and antispasmodics.

The following non-limitative examples are illustrative of the invention.

EXAMPLE I

5 1,6 - bis - (3 - Ethyl - 3 - phenyl - 1 - azetidine) - hexane.

10 Into a mixture of 10 g. of 3-ethyl-3-phenyl-azetidine and 10 ml. of trimethylamine 6 g. of adipyl chloride are gradually added without overcoming 0°. After standing for about half an hour the reaction mixture is poured into ice water and the precipitate is collected and dried. Yield 6.5 g. of adipyl-bis-3-ethyl-3-phenyl-1-azetidine, m.p. 149—150°.

15 The above intermediate is dissolved in 50 ml. of tetrahydrofuran, then a suspension of 3 g. of LiAlH₄ in 20 ml. of tetrahydrofuran is added. The mixture is warmed for 2.5 hours at about 5°, then it is treated

20 with a few millilitres of a 20 percent solution of ammonium chloride. After filtration the filtrate is dried over anhydrous sodium sulphate and evaporated to dryness. The residual oil crystallises on standing. Yield 6 g.,

25 m.p. 60—62°.

To obtain the bis methyl iodide 2.5 g. of the compound are dissolved in 50 ml. of anhydrous ethyl ether, then 1.76 g. of methyl iodide are added. A crystalline product 30 separates gradually and is collected and dried.

Yield 2.3 g., m.p. 100° (dec.).

EXAMPLE II.

1,6 - bis - (3,3 - Diethyl - 1 - azetidino)-hexane.

35 Into a mixture of 27 g. of 3,3-diethyl-azetidine and 25 ml. of triethylamine 22 g. of adipyl chloride are gradually added without exceeding 0°. After standing for about one hour the reaction mixture is poured into ice water and extracted with ethyl ether. The solvent is removed and the residual oil is distilled collecting at 200—210°/0.2 mm. Yield 30 g. of adipyl-bis-3,3-dimethylazetidide, m.p. 40—45°.

40 The above intermediate (3.25 g.) is dissolved in 20 ml. of tetrahydrofuran and hydrogenated with a suspension of LiAlH₄ in tetrahydrofuran as described in Example I. After evaporation of the solvent the residual oil is distilled collecting at 135—145°/0.2—0.4 mm. Yield 2.5 g.

45 The bis methyl iodide, prepared by the process of Example I, melts at 180—181° (dec.).

50 For the Applicants:—
GILL, JENNINGS & EVERY,
Chartered Patent Agents,
51/52 Chancery Lane,
London, W.C.2.

Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press.—1961.
Published by The Patent Office, 25, Southampton Buildings, London, W.C.2, from which
copies may be obtained.